CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-524/005

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA #:	20-524/SE1-005
Applicant:	Bertek
Name of Drug:	Mentax Cream 1%
Indication:	Treatment of tinea versicolor
Documents Reviewed:	Volumes 18.1, 18.9-18.14 dated August 7, 2000
Medical reviewer:	Brenda Vaughan, M.D. (HFD-540)
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I. INTRODUCTION AND BACKGROUND

The sponsor submitted reports of two Phase 3 studies, PDC 010-031 and PDC 010-032, to compare the safety and efficacy of Mentax (butenafine HCl) Cream 1%, versus its vehicle when used topically once daily for two weeks to treat tinea versicolor. Throughout this review, the terms Study 31, Study 32, and Mentax will be used instead of Study PDC 010-031, Study PDC 010-032, and Mentax (butenafine HCl) Cream, 1%. Studies 31 and 32 had identical designs.

II. STUDY DESIGN AND METHODS

This was a multicenter, double-blind, randomized, two-treatment-arm, parallel group study to compare the safety and efficacy of Mentax versus its vehicle when applied topically once daily for two weeks to treat tinea versicolor. Subjects with a clinical diagnosis of tinea versicolor confirmed by positive mycology (presence of hyphae in the KOH test), who met all additional entry criteria at the Day 1 visit, were enrolled into the study. The severity of the signs and symptoms of tinea versicolor (erythema, scaling, and pruritus) was assessed by the investigator. Subjects were then randomly assigned to one of two treatment arms (Mentax or the vehicle) at the ratio 2:1. Subjects were instructed to begin once daily treatment with the study medication and to continue applying the medication for 14 days. They were instructed to return to the study site at Week 2 (end of treatment) and at Weeks 4 and 8 (two and six weeks post treatment, respectively) for mycological and clinical assessments. Mycological and clinical assessments were made on all lesions identified visually. New lesions appearing within the two-week treatment period were included in the assessment of all lesions.

Inclusion Criteria were: Male or female, at least twelve years of age; clinical diagnosis of tinea versicolor confirmed by microscopy (KOH exam positive for the presence of hyphae); and Total severity score ≥3 for clinical signs and symptoms of tinea versicolor (erythema, scaling, pruritus).

Methods of Randomization and Blinding

Subjects were randomly assigned to one of the two treatment arms: Mentax or the vehicle. Treatments were allocated in blocks of three with a 2:1 ratio in favor of active treatment. Randomization was stratified by site and randomization codes were generated for each site. Randomization schedule was provided in the NDA. This was a double-blind study. All Mentax and vehicle formulations were supplied in identical, indistinguishable tubes.

Efficacy and safety variables

Subjects were evaluated clinically for the presence and severity of signs and symptoms of tinea versicolor and mycologically for the presence of hyphae. Subjects were examined by the investigator at Day 1, Day 15 (Week 2), Day 28 (Week 4) and Day 56 (Week 8) for signs and symptoms of tinea versicolor. At each visit the severity of erythema, scaling and pruritus was graded on a scale from 0 to 3 described in Table 1. Total Signs and Symptoms (TSS) score was the sum of these three individual scores and could range from 0 to 9.

Table 1. Severity of Erythema, Scaling and Pruritus: Definitions of Scores

Score	Severity	Erythema, Scaling	Pruritus
0	Absent	Absent	Absent
1	Mild	Minimal involvement	at least occasionally present but not bothersome to subject
2	Moderate	Distinctive presence	Present and bothersome Some of the time
3	Severe	Marked, intense	Present and so bothersome that the subject thinks about it much of the time

Negative Mycology was defined as the absence of hyphae in the KOH exam. The KOH exams were done on Days 1, 14, 28, and 56 or early termination (study exit).

Safety was assessed based on adverse events. At each visit, subjects were asked if they had experienced any medical problems since the last visit. The investigator recorded the adverse events observed or reported by the subject during and following study medication treatment.

Primary Efficacy Variable

According to the protocol, the primary efficacy variable was the proportion of subjects with Effective Treatment defined as Negative Mycology (the absence of hyphae in a KOH exam) plus Total Signs and Symptoms (TSS) score equal to 1 or 0 at Week 8/Day 56. Primary efficacy was assessed on Intent-to-Treat population (ITT). Primary efficacy was assessed considering all lesions (baseline lesions and new lesions appearing within two-week treatment period).

Secondary Efficacy Variables

Secondary efficacy variables included:

- The proportion of subjects with Negative Mycology of all lesions.
- The proportion of subjects with Complete Cure of all lesions (defined as Negative Mycology plus the Total Signs and Symptoms score of 0 at Week 8/Day 56).

Efficacy Populations

The sponsor's primary efficacy population was the **MITT Population** defined as all subjects with confirmed tinea versicolor who were dispensed study medication (active or vehicle). As there were no delayed exclusions in the pivotal studies, this reviewer will call this population the **ITT population** (instead of the MITT population).

The **Per-Protocol Population** was defined as all subjects who met entry criteria, were dispensed study medication and completed the study with no noteworthy protocol deviations, or who discontinued early due to treatment failure or treatment-related adverse events. Noteworthy protocol deviations included:

1. Failure to meet all inclusion/exclusion criteria
2. Failure to apply ≥50% required doses to all lesions
3. Use of disallowed medications at any period during the entire study period
4. End-of-Study visit <42 days or >63 Days after Day 1

The ITT and Per-protocol analyses differed in their handling of data from any new lesions that appeared after the baseline visit. For the ITT populations, "all lesions" included all lesions present at baseline and emergent during the fourteen-day treatment phase of the study. Lesions

that appeared after the treatment phase were not included. For the Per-Protocol population, "all lesions" included all lesions at baseline and lesions emergent during the study which received ≥ 7 doses of study medication. The severity score recorded for erythema, scaling or pruritus was the highest (worst) score of any lesion, irrespective of whether that lesion was present at baseline or emergent during the treatment. Similarly, both baseline and newly emergent lesions were potential sources for skin scrapings for mycological assessments.

Demographics and Baseline Comparisons

Treatment groups were assessed for balance at baseline. Comparability across treatment groups was done by a Fisher's exact test for nominal or dichotomous parameters, by a Wilcoxon rank-sum test for ordinal measurements and by a t-test for continuous measurements and the Total Signs and Symptoms score.

Efficacy Statistical Methods

Sponsor's Efficacy Analysis Methods

In agreement with the protocol, the primary efficacy analysis was performed on Effective Treatment considering all lesions at Week 8/study exit in the ITT population using a Fisher's exact test. Results were confirmed using Per-Protocol population. The between treatment differences for these endpoints were tested at the 0.05 significance level. In Study 31, two sites enrolled less than twenty subjects. These sites were pooled together.

In agreement with the protocol, the primary analysis with Fisher's exact test was confirmed using a logistic regression analysis for the same endpoint and population. The logistic regression models controlled for site, tinea versicolor duration since first occurrence, age, gender, race, and the baseline Total Signs and Symptoms (TSS). The final logistic regression included center if the center-by-treatment interaction was shown to be significant.

In agreement with the protocol, a variable was to be considered for inclusion in a model as a covariate if:

1. Baseline values of the variable were not comparable between treatment groups,
2. Baseline values of the variable explained within-group variability of an endpoint, (variable and endpoint were correlated) or,
3. The variable was considered medically relevant to the endpoint.

The sponsor's efficacy analyses for Negative Mycology and Complete Cure at Week 8/study exit used the same approach as the primary efficacy variable, Effective Treatment. A Fisher's exact

test was used for the primary analysis and logistic regression was used to confirm the results. The primary analysis population was the ITT population. All analyses were performed using this population and repeated using the Per-Protocol population.

For the ITT population, if the Week 8 data was missing, it was replaced by the last non-missing observation, including baseline observations. For the Per-Protocol population, if the Week 8 data was missing due to a treatment failure or a treatment related adverse event, it was replaced by the last non-missing observation, including baseline observations.

Reviewer's Comments:

1. The Sponsor's Statistical Methods

On page 4 of the minutes for the 1.11.99 EP2 meeting, the Division recommended that the primary efficacy analysis should be adjusted for center. In spite of that, the sponsor's primary efficacy analysis was the Fisher's exact test, with no adjustment for center. As a supporting analysis, the sponsor used logistic regression adjusting for six covariates. This reviewer believes that the sponsor's logistic regression method has the following deficiencies:

- **According to the protocol, final logistic regression included center only if the center-by-treatment interaction was shown to be significant.**
- **The sponsor's included six covariates in the model. The number of covariates should be limited.**
- **The sponsor's approach of selecting and dropping covariates from the model was quite arbitrary. According to the Agency's policy, analysis of covariance is an appropriate statistical method if a precise form of the model is pre-specified in the protocol.**

As this was not the case in this NDA, this reviewer used the CMH procedure adjusted for center as a primary efficacy method. In Study 31, center #2 had only 12 subjects and center #3 had 19 subjects. For this reason, this reviewer provided also a primary efficacy analysis with these two centers pooled together.

2. Variability of the KOH results in some subjects

The medical reviewer found that 9 subjects in Study 31 and 8 subjects in Study 32 had a variability in the KOH results, which made their negative mycology at Week 8 unreliable. For this reason, the medical reviewer requested this reviewer to perform an alternative efficacy analysis excluding these subjects.

3. Supportive Analysis of Target Lesions

In agreement with the Division's recommendation at the Pre-NDA meeting with the sponsor, analysis of all lesions is a primary efficacy analysis in this review. In addition, at the request of the medical reviewer, this review also provides a supportive analysis of target lesions. In the analysis of target lesions, the medical reviewer excluded 7 subjects in Study 31 and 5 subjects in Study 32, because these subjects had variability in the KOH results which made their negative mycology at Week 8 unreliable.

III. RESULTS OF STUDY 31

Table 1 shows the number of subjects included in the Safety, ITT, and Per-Protocol populations. A total of 129 subjects were randomized into Study 31, with 87 receiving Mentax and 42 receiving the vehicle. All randomized subjects had confirmed diagnoses of tinea versicolor and all were dispensed study medication. All 129 randomized subjects were included in the ITT population. Seven subjects did not provide any post-baseline data, four from the Mentax group and three from the vehicle group (p=0.56). These subjects were eliminated from the Safety population which consisted of 122 subjects, 83 in the Mentax group and 39 in the vehicle group.

Table 1: Subject Disposition in Study 31 by Treatment [a]

[Number of Subjects (% Randomized)]

	Mentax	Vehicle	P-value
Randomized	87 (100%)	42 (100%)	
ITT Population	87 (100%)	42 (100%)	1.00
Unconfirmed Tinea Versicolor	0 (0%)	0 (0%)	
Not Dispensed Study Medication	0 (0%)	0 (0%)	
Safety Population	83 (95%)	39 (93%)	0.56
Not Dispensed Study Medication	0 (0%)	0 (0%)	
No Post-baseline Data	4 (5%)	3 (7%)	
Per-Protocol Population	73 (84%)	38 (90%)	0.30

[a] Sponsor's Table 5, page 120, Volume 2, Sponsor's Submission.

This reviewer compared the randomization schedule and the subject listing and found no discrepancies in the treatment assignment. Eighteen subjects had major protocol violations and were excluded from the Per-Protocol population. Fourteen were in the Mentax group and four were in the vehicle group (p=0.3).

After these eighteen subjects were excluded, the Per-Protocol population consisted of 111 subjects, 73 in the Mentax group and 38 in the vehicle group. Of the total of 87 randomized Mentax subjects and 42 randomized vehicle subjects, 79 (91%) subjects receiving Mentax and 35 (83%) subjects receiving the vehicle completed the protocol (p=0.23). Three (3.4%) Mentax-treated subjects and four (9.5%) vehicle-treated subjects did not complete the study due to treatment failure (p=0.17). No subject failed to complete the study due to adverse events.

Demographic and other data

Demographic and clinical characteristics for all randomized subjects are displayed by treatment in Table 2. Age ranged from 15 to 77 years, overall. The mean age was similar (p=0.088) between the two treatment groups, 33.0 years and 32.6 years for Mentax and vehicle, respectively. Males comprised slightly more than half in each of the treatment groups, 53% of the Mentax group and 57% of the vehicle group (p=0.71). Caucasians made up more than two-thirds of both treatment groups, they comprised 71% of the Mentax group and 67% of the vehicle group (p=0.81). Clinical parameters of height, weight, pulse and systolic and diastolic blood pressure were similar between the two groups (p>0.46).

Table 2: Baseline Demographic Characteristics in Study 31[b]

(All Randomized Subjects)

	Mentax (N=87)	Vehicle (N=42)	P-value[a]
Age (years)			
Mean (sd)	33.0 (11.9)	32.6 (17.1)	0.879
Range	15, 65	15, 77	
Gender			
Male	46 (53%)	24 (57%)	0.708
Female	41 (47%)	18 (43%)	
Race			
Caucasian	62 (71%)	28 (67%)	0.807
Non-Caucasian	25 (29%)	14 (33%)	
Black	2 (2%)	1 (2%)	
Asian	2 (2%)	0 (0%)	
Hispanic	21 (24%)	13 (31%)	

[a] Fisher's Exact test performed for gender and races; t-test performed for age.

[b] Sponsor's Table 6, page 122, Volume 2, Sponsor's Submission.

Characteristics of the ITT Population

The primary efficacy analyses were performed on the ITT population. All 129 randomized subjects were included in the ITT population. The time since the onset of the current episode of tinea versicolor was similar between the two treatment groups, 15.1 months for the Mentax-treated group and 20.2 months in the vehicle-treated group (p=0.61). The time since the first episode of tinea versicolor was numerically longer for the Mentax-treated group than the vehicle-treated group (121.7 months and 79.3 months, respectively, p=0.06). The distribution of signs and symptoms (erythema, scaling and pruritus) was similar between the two groups (p>0.13).

Primary Efficacy Results in Study 31

The primary efficacy variable was proportion of patients with Effective Treatment of all lesions (Negative Mycology with a Total Signs and Symptoms score ≤ 1) at Week 8/study exit in the ITT population. Table 3 shows that at study exit (Week 8), 55% of the Mentax-treated group and 36% of the vehicle-treated group achieved Effective Treatment. As center #2 had only 12 subjects and center #3 had 19 subjects, this reviewer also performed the primary efficacy analysis with these two centers pooled. In the reviewer's primary efficacy analysis of the ITT population, Mentax was statistically significantly better than vehicle with p=0.039 and p=0.038 in the non-pooled and pooled analyses, respectively.

Table 3: Primary Efficacy Analysis in Study 31

Effective Treatment of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P-value	CMH-test[b] P-value
Original analysis (the ITT population)	48/87 (55%)	15/42 (36%)	19%	0.041	0.028	**0.039** **0.038**(pooled)[d]
Alternative analysis excluding 9 subjects[c]	40/79 (51%)	14/41 (34%)	17%	0.121	-	**0.084** **0.082** (pooled)[d]

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

[c] Eight Mentax subjects (T103, T104, T116, T404, T407, T411, T418, and T529) and one Vehicle subject (T416) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

[d] Analysis with small sites #2 and # 3 pooled.

The medical reviewer found that 9 subjects in Study 31 had a great variability in the KOH results, which made their negative mycology at Week 8 unreliable. For this reason, the statistical reviewer also performed an alternative efficacy analysis excluding these 9 subjects. Relative to the proportion of patients with Effective Treatment, in the analysis excluding these 9 patients, Mentax was only numerically better than vehicle with p=0.084 and p=0.082 in the non-pooled and pooled analyses, respectively.

In the reviewer's CMH test in the Per Protocol population, Mentax was only numerically better than vehicle (p=0.063). In the sponsor's primary efficacy analysis of the ITT population, the difference between the treatment groups was statistically significant: p=0.041 in Fisher's exact test and p=0.028 in the logistic regression model.

Supportive Analysis of Target Lesions

To support the primary efficacy analysis of all lesions, Table 3A presents analysis of Effective Treatment of target lesions. Table 3A shows that at Week 8/study exit, 60% of the Mentax-treated group and 38% of the vehicle-treated group achieved Effective Treatment of target lesions (p=0.023 in the CMH test).

Table 3A: Supportive Efficacy Analysis in Study 31

Effective Treatment of Target Lesions at Week 8, by Treatment

[Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	52/87 (60%)	16/42 (38%)	22%	0.025	0.011	**0.023**
Alternative analysis excluding 7 subjects[c]	47/82 (57%)	14/40 (35%)	22%	0.033	-	**0.022**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

[c] Five Mentax subjects (T116, T404, T407, T410, and T411) and two Vehicle subjects (T109 and T416) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

In the analysis of target lesions of Study 31, the medical reviewer excluded 7 subjects, because these subjects had variability in the KOH results, which made their negative mycology at Week 8 unreliable. Table 3A shows that in the CMH analysis excluding 7 patients with unreliable negative mycology, Mentax was statistically significantly better than vehicle (57% vs. 35%, p=0.022).

Secondary Efficacy Analysis in Study 31

Complete Cure

A summary of subjects achieving Complete Cure of all lesions is presented in Table 4. Numerically greater percentages of subjects in the Mentax-treated group achieved Complete Cure at Week 8/study exit (51% vs. 36%). This difference was not statistically significant in either reviewer's CMH test (p=0.113), or sponsor's Fisher's exact test (p=0.133), or in the logistic regression analysis (p=0.066).

Table 4: Secondary Efficacy Analysis in Study 31

Complete Cure of All Lesions at Week 8, by Treatment

[Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	44/87 (51%)	15/42 (36%)	15%	0.133	0.066	**0.113**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).
[b] CMH test controlling for site (reviewer's analysis).

Negative Mycology

Table 5 shows that at study exit (Week 8), 55% of the Mentax-treated group and 36% of the vehicle-treated group achieved Negative Mycology. This difference was statistically significant in reviewer's CMH test (p=0.039), and in sponsor's Fisher's exact test (p=0.041), and in the logistic regression analysis (p=0.028).

Table 5: Secondary Efficacy Analysis in Study 31

Negative Mycology at Week 8, by Treatment

[Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	48/87 (55%)	15/42 (36%)	19%	0.041	0.028	**0.039**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

Subgroup Analysis in Study 31

Table 6 summarizes the number and percent of subjects in the ITT population achieving Effective Treatment of all lesions at Week 8/study exit for age, gender, and race subgroups. It should be noted that the study was not designed to test efficacy within subgroups. Mentax was statistically significantly better than its vehicle in males (p=0.020) and Caucasians (p=0.022), and marginally significantly better in the subgroup of patients 18-36 years of age (p=0.056).

Table 6: Subgroup Comparisons of Effective Treatment

[Number Achieved (% achieved)] – ITT Population of Study 31

Subgroup	Mentax	Vehicle
Age		
<18	1/5 (20%)	0/4 (0%)
18-36	30/49 (61%)	9/ 24 (38%)
37-56	17/31 (55%)	4/10 (40%)
57-64	0/2 (0%)	0/0 (0%)
≥ 65	0/0 (0%)	2/4 (50%)
Gender		
Male	24/46 (52%)	5/24 (21%)
Female	24/41 (59%)	10/18 (56%)
Race		
Caucasian	37/62 (60%)	9/28 (32%)
Non-Caucasian	11/25 (44%)	6/14 (43%)
Black	0/2 (0%)	0/1 (0%)
Asian	2/2 (100%)	0/0 (0%)
Hispanic	9/21 (43%)	6/13 (46%)

Safety in Study 31

Of the 129 subjects randomized into the study, 122 (95%) provided post-baseline data and were included in the Safety Population. The Safety Population was evaluated for the incidence of adverse events. Eighteen subjects (13 [16%] in the Mentax group and 5 [13%] in the vehicle group) experienced adverse events (p=0.789). None of the reported adverse events were considered by the physicians to have relationship to study treatment. There were no reported deaths and no subject withdrew from the study due to an adverse event.

Conclusions on Study 31

The ITT population in Study 31 included 87 Mentax subjects and 42 vehicle subjects. The primary efficacy variable was Effective Treatment of all lesions (Negative Mycology with a Total Signs and Symptoms score ≤ 1) at Week 8/study exit. The reviewer's primary statistical method was the CMH test controlling for center. As center #2 had only 12 subjects and center #3 had 19 subjects, this reviewer also performed the primary efficacy analysis with these two centers pooled. In the primary efficacy analysis of the ITT population, Mentax was statistically significantly better than vehicle with p=0.039 and p=0.038 in the non-pooled and pooled analyses, respectively. In the analysis excluding 9 patients with unreliable negative mycology at Week 8, Mentax was only numerically better than vehicle with p= 0.084 and p=0.082 in the non-pooled and pooled analyses, respectively. There was no statistically significant difference between the treatment groups relative to the proportion of patients with adverse events (p=0.79).

IV. RESULTS OF STUDY 32

A total of 129 subjects were randomized, 86 receiving Mentax and 43 receiving the vehicle. Seventy-seven of 86 (90%) subjects receiving Mentax and 40 of 43 (93%) subjects receiving the vehicle completed the protocol (p=0.51). No subject failed to complete the study due to treatment failure or an adverse event. Table 7 shows the number of subjects included in the Safety, ITT, and Per-Protocol populations. All randomized subjects had confirmed diagnoses of tinea versicolor and all were dispensed study medication. All 129 randomized subjects were included in the ITT population. This reviewer compared the randomization schedule and the subject listing and found no discrepancies in the treatment assignments.

Table 7: Subject Disposition in Study 32, by Treatment [a]

[Number of Subjects (% Randomized)]

	Mentax	Vehicle	P-value
Randomized	86 (100%)	43 (100%)	
ITT Population	86 (100%)	43 (100%)	1.0
Unconfirmed Tinea Versicolor	0 (0%)	0 (0%)	
Not Dispensed Study Medication	0 (0%)	0 (0%)	
Safety Population	81 (94%)	41 (95%)	0.078
Not Dispensed Study Medication	0 (0%)	0 (0%)	
No Post-baseline Data	5 (6%)	2 (5%)	
Per-Protocol Population	71 (83%)	40 (93%)	0.089

[a] Sponsor's Table 5, page 085, Volume 5, Sponsor's Submission.

Seven subjects did not provide any post-baseline data, five from the Mentax group and two from the vehicle group (p=0.078). These subjects were eliminated from the Safety population which consisted of 122 subjects, 81 (94%) in the Mentax group and 41 (95%) in the vehicle group.

Eighteen subjects had major protocol violations and were excluded from the Per-Protocol population. Fifteen (17%) were in the Mentax group and three (7%) were in the vehicle group (p=0.089).

Demographic and clinical characteristics for all randomized subjects are displayed by treatment in Table 8. Age ranged from 13 to 75 years overall, and the mean age was similar (p=0.16) between the two treatment groups, 35.7 and 32.1 years for Mentax and vehicle, respectively. Males comprised slightly more than half (58%) of both treatment groups. Caucasians made up more than three-quarters of both treatment groups, they comprised 77% of the Mentax group and 79% of the vehicle group (p=0.64). Blacks comprised 16 % of both treatment groups. Clinical parameters of height, weight, pulse and systolic and diastolic blood pressure were similar between the two groups (p>0.08).

Table 8: Baseline Demographic Characteristics by Treatment [b]
All Randomized Subjects in Study 32

	Mentax (N=86)	Vehicle (N=43)	P-value[a]
Age (years)			
Mean (sd)	35.7 (12.9)	32.1 (14.5)	0.160
Range	13, 75	14, 75	
Gender			
Male	50 (58%)	25 (58%)	1.00
Female	36 (42%)	18 (42%)	
Race			
Caucasian	66 (77%)	34 (79%)	0.639
Non-Caucasian	20 (23%)	9 (21%)	
Black	14 (16%)	7 (16%)	
Asian	0 (0%)	1 (2%)	
Hispanic	5 (6%)	1 (2%)	
Other	1 (1%)	0 (0%)	

[a] Fisher's Exact test performed for gender and race; t-test performed for age.

[b] Sponsor's Table 6, page 087, Volume 5, Sponsor's Submission.

Primary Efficacy Analysis in Study 32

Effective Treatment

The primary efficacy variable was Effective Treatment of all lesions (Negative Mycology with a Total Signs and Symptoms score ≤ 1) at Week 8/study exit in the ITT population. Table 9 shows that at Week 8/study exit, 43% of the Mentax-treated group and 26% of the vehicle-treated group achieved Effective Treatment of all lesions. In the reviewer's CMH test in the ITT population, Mentax was marginally significantly better than vehicle (p=0.051). In the sponsor's analysis, p=0.057 in the Fisher's exact test, and p=0.086 in the logistic regression model. In the reviewer's analysis excluding 8 patients with unreliable negative mycology, Mentax was statistically significantly better than vehicle (40% vs. 20%, p=0.030).

Table 9: Primary Efficacy Analysis in Study 32

Effective Treatment of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	37/86 (43%)	11/43 (26%)	17%	0.057	0.086	**0.051**
Alternative analysis excluding 8 subjects[c]	32/81 (40%)	8/40 (20%)	20%	0.040	-	**0.030**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

[c] Five Mentax subjects (V111, V218, V401, V424, and V508) and three Vehicle subjects (V207, V210, and V505) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

Supportive Analysis of Target Lesions

To support the primary efficacy analysis of all lesions, Table 9A provides analysis of Effective Treatment of target lesions. Table 9A shows that at Week 8/study exit, 58% of the Mentax-treated group and 33% of the vehicle-treated group achieved Effective Treatment of target lesions (p=0.007 in the CMH test). In the analysis of target lesions of Study 32, the medical reviewer excluded 5 subjects, because these subjects had variability in the KOH results, which made their negative mycology at Week 8 unreliable. Table 9A shows that in the CMH analysis excluding 5 patients with unreliable negative mycology, Mentax was statistically significantly better than vehicle (56% vs. 31%, p=0.008).

Table 9A: Supportive Efficacy Analysis in Study 32

Effective Treatment of Target Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	50 /86 (58%)	14/43 (33%)	25%	0.009	0.013	**0.007**
Alternative analysis excluding 5 subjects[c]	46/82 (56%)	13 /42 (31%)	25%	0.013	-	**0.008**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

[c] Four Mentax subjects (V401, V424, V504, and V507) and one Vehicle subject (V505 were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

Secondary Efficacy Analysis in Study 32

Complete Cure

A summary of subjects achieving Complete Cure of all lesions at week 8 is presented in Table 10. Mentax was only numerically better than vehicle in the ITT population of Study 32, (35% vs. 23%, p=0.16 in the reviewer's analysis, p=0.23 in the sponsor's Fisher's exact test, and p=0.006 in the logistic regression). Analysis in the Per Protocol population supported the results in the ITT population (p>0.2).

Table 10: Secondary Efficacy Analysis in Study 32

Complete Cure of All Lesions at Week 8, by Treatment

[Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	30/86 (35%)	10/43 (23%)	12%	0.227	0.006	**0.16**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

[b] CMH test controlling for site (reviewer's analysis).

Negative Mycology

Negative Mycology of all lesions is summarized for the ITT population in Table 11. In the ITT population of Study 32, a total of 50% of the Mentax-treated group and 28% of the vehicle-treated group achieved Negative Mycology at Week 8. This difference was statistically significant in the reviewer's analysis (p=0.015), and in the sponsor's analysis (p= 0.023 in the Fisher's exact test, and p=0.034 in the logistic regression model).

Table 11: Secondary Efficacy Analysis in Study 32

Negative Mycology at Week 8, by Treatment
[Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model[a] P–value	CMH-test[b] P –value
Original analysis (the ITT population)	43/86 (50%)	12/43 (28%)	22%	0.023	0.034	**0.015**

[a] Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis)

[b] CMH test controlling for site (reviewer's analysis).

Subgroup analysis in Study 32

Table 12 summarizes the number and percent of subjects in the ITT population of Study 32 achieving Effective Treatment of all lesions at Week 8/study exit for age, gender, and race subgroups. It should be noted that the study was not designed for testing the differences within subgroups. Mentax was statistically significantly better than its vehicle in the following

subgroups: males (p=0.020), Caucasians (p=0.022), and subjects of 37-56 years of age (p=0.016).

Table 12: Summary of Subgroup Comparisons of Effective Treatment [Number Achieved (% achieved)] – ITT Population of Study 32

Subgroup	Mentax	Vehicle
Age		
<18	4/10 (40%)	2/6 (33%)
18-36	11/32 (34%)	7/26 (27%)
37-56	22/42 (52%)	1/9 (11%)
57-64	0/1 (0%)	0/0 (0%)
≥ 65	0/1 (0%)	1/2 (50%)
Gender		
Male	18/50 (36%)	6/25 (24%)
Female	19/36 (53%)	5/18 (28%)
Race		
Caucasian	31/66 (47%)	8/34 (24%)
Non-Caucasian	6/20 (30%)	3/9 (33%)
Black	6/14 (43%)	2/7 (29%)
Asian	0/0 (0%)	0/1 (0%)
Hispanic	0/5 (0%)	1/1 (100%)
Other	0/1 (0%)	0/0 (0%)

Safety in Study 32

Of the 129 subjects randomized into the study, 122 (95%) provided post-baseline data and were included in the Safety Population. The Safety Population was evaluated for the incidence of adverse events. A total of 14 subjects (8 [10%] in the Mentax group and 6 [15%] in the vehicle group) experienced adverse events (p=0.548).

Conclusions on Study 32

The ITT population in Study 32 included 86 Mentax subjects and 43 vehicle subjects. The primary efficacy variable was proportion of patients with Effective Treatment of all lesions. The reviewer's primary statistical method was the CMH test controlling for center. In the reviewer's primary efficacy analysis of the ITT population, Mentax was marginally significantly better than vehicle (43% vs. 26%, p=0.051). In the sponsor's analysis, p=0.057 in the Fisher's exact test, and p=0.086 in the logistic regression model. In the reviewer's analysis excluding 8 patients with unreliable negative mycology at Week 8, Mentax was statistically significantly better than vehicle (40% vs. 20%, p=0.030). There was no statistically significant difference between the treatment groups relative to the proportion of patients with adverse events (p=0.55).

V. A SUMMARY TABLE FOR THE LABEL

The following table is proposed to summarize the pivotal studies results in the label:

Proportion (%) of responders in pivotal clinical trials (all randomized patients)					
Patient Response Category	Week	Study PDC 010-031		Study PDC 010-032	
		Mentax	Vehicle	Mentax	Vehicle
Complete Cure[@] Of all lesions	2*	41/87 (47%)	11/40 (28%)	29/85 (34%)	12/41 (29%)
	4[©]	43/86 (50%)	15/42 (36%)	36/83 (43%)	13/41 (32%)
	8[©]	44/87 (51%)	15/42 (36%)	30/86 (35%)	10/43 (23%)
Effective Treatment[#] Of all lesions	2*	56/87 (64%)	16/40 (40%)	46/85 (54%)	16/41 (39%)
	4[©]	50/86 (58%)	19/42 (45%)	45/83 (54%)	16/41 (39%)
	8[©]	48/87 (55%)[§]	15/42 (36%)	37/86 (43%)	11/43 (26%)
Negative Mycology Of all lesions	2*	57/87 (66%)	20/40 (50%)	57/85 (67%)	21/41 (51%)
	4[©]	51/86 (59%)	20/42 (48%)	52/83 (63%)	18/41 (44%)

	8©	48/87 (55%)§	15/42 (36%)	43/86 (50%)	12/43 (28%)

§ Statistically significant difference between the Mentax and Vehicle groups.

* End of treatment.

© Post-treatment visit.

@ Negative Mycology plus absence of erythema, scaling, and pruritus.

Negative Mycology plus no or minimal involvement of erythema and scaling plus no or only occasionally present pruritus (not bothersome to patient).

VI. REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor):

The sponsor submitted reports of two Phase 3 studies, PDC 010-031 and PDC 010-032, to compare the safety and efficacy of Mentax Cream versus its vehicle when used topically once daily for two weeks in the treatment of tinea versicolor. The primary efficacy variable was proportion of patients who achieved Effective Treatment of all lesions (Negative Mycology with a Total Signs and Symptoms score ≤ 1) at Week 8/study exit in the ITT population.

The secondary efficacy variables were Complete Cure (Negative Mycology with a Total Signs and Symptoms score = 0) and Negative Mycology at Week 8/study exit. The reviewer's and the sponsor's statistical methods for the primary efficacy analysis were different. The sponsor's primary efficacy method was Fisher's exact test (no adjustment for center). The sponsor's supporting analysis was a logistic regression model adjusting for six covariates. The sponsor's method of selecting and dropping covariates was quite arbitrary. For this reason, this reviewer used the CMH procedure adjusted for center as a primary statistical method.

The medical reviewer found that 9 subjects in Study 31 and 8 subjects in Study 32 had variability in the KOH results, which made their negative mycology at Week 8 unreliable. For this reason, the statistical reviewer also performed an alternative efficacy analysis excluding these subjects.

In agreement with the Division's recommendation at the Pre-NDA meeting, analysis of all lesions is a primary efficacy analysis in this review. In addition, at the request of the medical reviewer, this review also provides a supportive analysis of target lesions. In the analysis of

target lesions, the medical reviewer excluded 7 subjects in Study 31 and 5 subjects in Study 32, because these subjects had variability in the KOH results, which made their negative mycology at Week 8 unreliable. This review also provides results for the target lesions excluding these patients with unreliable negative mycology at Week 8.

Study PDC 010-031

The ITT population in Study 31 included 87 Mentax subjects and 42 vehicle subjects. In the reviewer's primary efficacy analysis of Effective Treatment of all lesions in the ITT population, Mentax was statistically significantly better than vehicle (55% vs. 36%, p=0.039). The sponsor's analysis also produced statistically significant results: p=0.041 in Fisher's exact test, and p=0.028 in the logistic regression model.

In the reviewer's alternative analysis of Effective Treatment of all lesions excluding 9 patients with unreliable negative mycology at Week 8, Mentax was only numerically better than vehicle (51% vs. 34%, p=0.084).

In the reviewer's supportive analysis of Effective Treatment of target lesions, Mentax was statistically significantly better than vehicle (60% vs. 38%, p=0.023). In the reviewer's supportive analysis of Effective Treatment of target lesions excluding 7 patients with unreliable negative mycology at Week 8, Mentax was statistically significantly better than vehicle (57% vs. 35%, p=0.022).

There was no statistically significant difference between the treatment groups relative to the proportion of patients with adverse events (p=0.79).

Study PDC 010-032

The ITT population in Study 32 included 86 Mentax subjects and 43 vehicle subjects. In the reviewer's primary efficacy analysis in the ITT population, Mentax was only marginally significantly better than vehicle (43% vs. 26%, p=0.051) relative to the proportion of subjects with Effective Treatment of all lesions at Week 8. In the sponsor's primary efficacy analysis, p=0.057 in the Fisher's exact test, and p=0.086 in the logistic regression model.

In the reviewer's alternative analysis of Effective Treatment of all lesions excluding 8 patients with unreliable negative mycology at Week 8, Mentax was statistically significantly better than vehicle (40% vs. 20%, p=0.030).

In the reviewer's supportive analysis of Effective Treatment of target lesions, Mentax was statistically significantly better than vehicle (58% vs. 33%, p=0.007). In the reviewer's supportive analysis of Effective Treatment of target lesions excluding 5 patients with unreliable negative mycology at Week 8, Mentax was statistically significantly better than vehicle (56% vs. 31%, p=0.008).

There was no statistically significant difference between the treatment groups relative to the proportion of patients with adverse events (p=0.55).

Overall Conclusions:

The reviewer's primary efficacy analysis of the proportion of subjects with Effective Treatment of all lesions showed that Mentax (butenafine HCl cream) Cream 1% was statistically significantly better than vehicle in Study PDC 101-31 (p=0.039) and marginally significantly better than vehicle in Study PDC 010-32 (p=0.051). In the reviewer's alternative analysis of Effective Treatment of all lesions, which excluded patients with unreliable negative mycology at Week 8, Mentax was only numerically better than vehicle in Study PDC 101-31 (p=0.084) and statistically significantly better than vehicle in Study PDC 101-32 (p=0.030).

In both pivotal studies, there was no statistically significant difference between the treatment groups relative to the proportion of patients with adverse events (p≥0.55).

This is a matter of the clinical judgement of the medical division to decide whether Mentax (butenafine HCl) Cream 1% should be approved given the efficacy results described above.

/S/ 4/30/01

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cc:
Archival NDA 20-524/SE1-005
HFD-540
HFD-540/Mr. Cross
HFD-540/Dr. Vaughan
HFD-540/Dr. Luke
HFD-540/Dr. Wilkin
HFD-725/Dr. Alosh
HFD-725/Dr. Huque
HFD-700/Dr. Anello
HFD-725/Dr. Freidlin
Chron. (HFD-725)
This review contains 22 pages.